REMARKS

This application is amended in a manner to place it in condition for allowance at the time of the next Official Action.

Status of the Claims

Claim 1 is no directed to a composition comprising (a) an antigen and (b) an immunoadjuvant wherein said immunoadjuvant compound consists of a Rho GTPase activator belonging to the protein families of DNT and CNF1.

Claim 2 is now directed to a vaccine composition comprising (a) an antigen and (b)an immunoadjuvant wherein said immunoadjuvant consists of a Rho GTPase activator selected from the group consisting of : a polypeptide comprising the amino acid sequence starting at the amino acid residue 720 and ending at the amino acid residue 1014 of sequence SEQ ID NO 1, a polypeptide comprising the amino acid sequence starting at the amino acid residue 720 and ending at the amino acid residue 1014 of sequence SEQ ID NO 2, a polypeptide comprising the amino acid sequence starting at the amino acid residue 720 and ending at the amino acid residue 1014 of sequence SEQ ID NO 3, and a polypeptide comprising the amino acid sequence starting at the amino acid residue 1146 and ending at the amino acid residue 1451 of sequence SEQ ID NO 4.

Claim 3 is now amended to recite "SEQ ID NO", as suggested in the Official Action.

In claim 4, the "injection domain" and the "catalytic domain" of Rho GTPase are fully clarified since the polypeptide sequences have been added. Additionally, the term "antigen" has been added in order to better characterize the vaccine composition.

In claim 15, the terms "comprising" and "polypeptide" have been replaced by "composition" and "immunoadjuvant" in order to clarify the claimed invention.

Claims 8-10 have been amended with respect to their dependency.

Support for the amendment may be found generally throughout the specification, and the examples.

Claims 5-7, 11, 14 and 16 have been cancelled.

Claims 1-4, 8-10 and 15 remain in this application.

Claim Rejections-35 USC §112

Claims 1, 4-11 and 14-16 were rejected under 35 U.S.C. §112, second paragraph, for being indefinite. This rejection is respectfully traversed for the reasons below.

The position of the Official Action is that that Claim 1 and Claim 4 are vague and indefinite since the terms "RhoGTPase activator", "injection domain" and "catalytic domain" are unclear.

Claim 1 has been amended to recite that the appropriate

RhoGTPase activators belong to the protein families of DNT and CNF1. Thus, "RhoGTPase activators" is now definite, as DNT and CNF1 are clearly described in the present specification and since "Protein family" is a well-known concept for the one skilled in the art. That is, “proteins family” encompasses proteins which descend from a common ancestor and have similar functions, and significant sequence similarity.

Moreover, structural properties have been introduced to claims 2 and 4 to further describe the "Rho GTPase activators", the "injection domains" and the "catalytic domain" in a definite manner within the scope of the present invention.

Therefore, withdrawal of the rejection is respectfully requested.

Claim Objections

Claims 2, 3, 5, 6, and 14 were objected to for including informalities, such as unclear dashes and commas and confusing sequence identification number notation. The claims are amended in a manner to correct these informalities, and withdrawal of the objection is respectfully requested.

Claim Rejections-35 USC §102

Claims 1-6, 9-11 and 14-16 were rejected under 35 U.S.C. §102(b) as being anticipated by any of FELMLEE et al., FALBO et al., BUETOW et al., OSWALD et al., WALKER et al., SHARP

et al., PULLINGER et al., MIROLD et al. (1999), MIROLD et al.(2001), PARKHILL et al., BAKSHI et al., STENDER et al., MCCLELLAND et al., EHRBAR et al., LAN et al., SMITH et al., RON et al., KOMAI et al., EVA et al., and SHUNICHI et al. The rejections are respectfully traversed for the reasons below.

The claimed invention provides a new vaccine composition comprising a Rho GTPase activator as an immunoadjuvant and an antigen. The appropriate Rho GTPase activators belong to CNF1 and DNT protein families or are derived from CNF1, CNF2, CNFY and DNT proteins.

The documents cited in the Official Action describe either structural studies of Rho GTPase activators or genomic studies of bacteria having Rho GTPase activators. None of these documents describe vaccine composition resulting from the specific combination of (i) an antigen and (ii) a RhoGTPase activator as an immunoadjuvant.

Consequently, none of documents anticipate the claimed invention.

Moreover, none of these cited documents deal with vaccination and, thus, fail to suggest that Rho GTPase activator has immunoadjuvant properties. Thus, even when combined together, the teachings of the documents fail to incite one of ordinary skill in the art to develop the vaccine composition according to the claimed invention.

Consequently, the pending claims are not rendered obvious by the cited documents.

Therefore, withdrawal of the rejection is respectfully requested.

Claim Rejections-35 USC §112 Enablement

Claims 1-11 and 14-16 were rejected under 35 U.S.C. §112, first paragraph, for not complying with the enablement requirement.

This rejection is respectfully traversed for the reasons below, which explain why Rho GTPase activators and an anti VIH vaccine composition are enabled by present specification:

Rho GTPase activators

The position of the Official Action was that the examples provided with CNF1 and DNT are insufficient to include Rho GTPase activators in general in the scope of the present invention since the structure of Rho GTPasse activators varies greatly.

However, it is respectfully submitted that the immunoadjuvant properties of Rho GTPase activators do not result from their structural properties. This fact is illustrated by the examples of the present application which describe that:

- DNT and CNF1 both provide immunoadjuvant effect in

spite of their low sequence identity

- The catalytic domain of DNT is sufficient to stimulate anti-OVA immune responses in mice (see example 6)
- The inactivated mutant which differs from native CNF1 in virtue of a single amino acid mutation (C866S) has no immunoadiuvant property though its tertiary structure is identical to CNF1.

These experimental results clearly demonstrate that the immunoadjuvant property of Rho GTPase activators is due to their catalytic activity. Consequently, any Rho GTPase activator can provide an immunoadjuvant effect.

Moreover, the present specification provides a clear definition of the "RhoGTPase activator activity" (see p. 9 of the specification) and describes a method for evaluating this catalytic activity by the detection of activated Rho GTPase. It also comprises *in vitro* and *in vivo* evaluations of Rho GTPase activators as immunoadjuvant.

Thus, the present specification provides enough details to enable the one skilled in the art to understand and carry out the invention.

However, in order to expedite the grant of the present application, the Applicants concede to restrict the scope of the claims to Rho GTPase activators which belong to the protein families of CNF1 and DNT.

Actually, since DNT and CNF1 have a very low sequence identity combined with a similar immunoadjuvant property, the one skilled in the art can reasonably conclude that Rho GTPase activators which further have a high sequence identity with CNF1 or DNT are appropriate immunoadjuvants according to the invention. For example, CNFY (SEQ ID NO 3) and CNF2 (SEQ ID NO 3) are 60% and 84% identical to CNF1, respectively.

Furthermore, at the filing date of the present application, the one skilled in the art knew that CNF1 and DNT share common features. As illustrated by BUETOW *et al.* (Nature Structure Biology, 2001, 8:p.584-588, in particular p.584-585), CNF1 and DNT activate Rho family members through an identical catalytic mechanism, i.e., site specific deamidation of Gin residue to Glu and have structural similarities in their catalytic domains.

Anti-VIH vaccine composition

The position of the Official Action was that there is no known working vaccine to prevent HIV, and, thus, one of ordinary skill in the art allegedly could not use any HIV antigen and any Rho GTpase activator to develop an effective vaccine composition against AIDS without undue experimentation.

Firstly, the aim of the claimed invention is to provide

immunoadjuvants and not new antigens. As shown in the prior art, immunoadjuvants can be generally used with any appropriate adjuvant.

Secondly, despite the fact that there is no commercially available vaccine against HIV, many scientific publications describe efficient anti-HIV vaccines. For illustrative purpose, some of them are enclosed in the appendix of this amendment.

The first group of enclosed scientific publications describes vaccine comprising Tat toxoid(inactivated Tat protein of HIV). Clinical trials have shown that the administration of this vaccine is able to prevent or inhibit the development of immunosuppression, Kaposi's sarcoma and AIDS disease in seropositive patients. The potency of anti-Tat therapeutic vaccination is confirmed by several clinical trials, as described in the enclosed documents.

The second group of scientific publications describes a vaccine comprising lipopeptides derived from Nef, Gag and Env proteins of HIV-1. The phase I clinical trials have shown that the said vaccine is well-tolerated and allows to induce the production of IgG against HIV proteins and the activation of CD4+ and CD9+ T cells.

Moreover, as described in BioNest data base (bionext.com) and in the US National Institute of Health Clinical Trials website (clinicaltrials.gov), several clinical trials

concerning HIV vaccines are in progress or will begin soon. For illustrative purposes, some data sheets obtained from these websites are also included in the appendix.

As demonstrated above, several effective HIV antigens are available. Accordingly, one of ordinary skill in the art could prepare an anti-HIV vaccine composition by combining a Rho Gtpase activator with guidance from the present application with any one of the effective HIV antigens described in the prior art without undue Experimentation.

Therefore, the claims do comply with the enablement requirement, and withdrawal of the rejection is respectfully requested.

Conclusion

In view of the amendment to the claims and the foregoing remarks, this application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our credit card which is being paid online simultaneously herewith for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

- Buetow, L. et al., "Structure of the Rho-activating domain of *Escherichia coli* cytotoxic necrotizing factor 1", Nature Structural Biology", Vol. 8, No. 7, July 2001, pp. 584-588.

- Gahéry-Ségard, H. et al., "Multiepitopic B- and T-Cell Responses Induced in Humans by a Human Immunodeficiency Virus Type 1 Lipopeptide Vaccine", Journal of Virology, Vol. 74, No. 4, Feb. 2000, pp. 1694-1703.

- Gahéry-Ségard, H. et al., "Long-Term Specific Immune Responses Induced in Humans by a Human Immunodeficiency Virus Type 1 Lipopeptide Vaccine: Characterization of CD8+-T-Cell Epitopes Recognized", Journal of Virology, Vol. 77, No. 20, Oct. 2003, pp. 11220-11231.

- Clumeck, N. et al., (Oral Presentation) "Neutralizing anti-Tat antibodies prolonged HAART interruption in vaccines in a prospective structured interruption study", Retrovirology, page 1 of 1.

- Meeting Abstracts, International Meeting of the Institute of Human Virology, Baltimore, MD (Sept. 9-13, 2001; Sept. 10-15, 2000)

- Gringeri, A. et al., "Safety and Immunogenicity of HIV-1 Tat Toxoid in Immunocompromised HIV-1-Infected Patients", Journal of Human Virology, Vol. 1, No. 4, May/June 1998, pp. 293-298.

- Clinical Trials.gov. U.S. National Institute of Health, Study Summaries ("HIV Vaccine Trial in Thai Adults", "Phase 1 Safety Study of Two Experimental HIV Vaccines", "HIV-1 Vaccine Test in Uninfected Adult Volunteers").

- Nextbio.com. Clinical Trial > Reactogenicity and Immunogenicity of Vaginal ZM96gp 140.